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Alpha Emitter Therapy of Leukemia and Other Cancers

The full therapeutic impact of radioimmunotherapy has been in part limited by the long range of the beta particles, emitted by the most currently used isotopes in the field. Alpha emitting isotopes are therefore of particular interest because of their unique characteristics, which include extremely high energy coupled with very short range of the particles. The resulting energy is characterized by very high LET (linear energy transfer). In principle, an alpha particle can kill a single cancer cell, while not harming a normal cell next to it. As much as 8 million electron volts of energy is deposited in a path no longer than the length of 2 or 3 tumor cells. As a consequence of this extraordinary deposition of energy, only a single alpha particle is needed to kill a cancer cell making it the most cytotoxic agent available. Our research over the last decade has focused on developing methods to successfully and efficiently target alpha emitting isotopes to tumors, to stably link the isotope to the antibody targeting vehicle, and to develop a reliable source of isotope that might be used feasibly in patients.

Our initial efforts have focused on acute myeloid leukemia, prostate cancer, and non-Hodgkin's lymphomas. Antibodies that selectively target these types of cancer have been identified and conjugated to bifunctional chelates capable of containing Bi-213, a short lived, alpha emitting isotope. The first of these agents (213 bismuth-CHX-A-DTPA-HuM195) has entered human clinical trials. Seventeen patients have been treated to date in a Phase I dose escalation trial, which has demonstrated safety and tolerability of the agent, rapid and efficient targeting of the alpha particle directly to the cancer cells followed by death of those cells. No significant extramedullary toxicity has been seen in these patients, and dose escalation continues. Alpha emitting antibodies in the area of prostate cancer and lymphoma are now in preclinical testing. Anti-tumor activity has now been demonstrated *in vitro* and in animal models of these diseases. Based on the characteristics of the alpha particle emissions and the preclinical and clinical data, it appears that the most advantageous use for this form of radioimmunotherapy will be in the elimination of minimal disease, reduction of micrometastatic disease, or in attacks on single cell cancers, such as leukemias. Moreover, the short half-lives of the isotopes and the short path lengths of the alpha particles result in no waste issues for the use of the agents in hospitals.